

Cancer is a disease driven by DNA alterations. These include somatic mutations (de novo mutations in the tissue of tumor origin), novel gene fusions, gene copy number changes, DNA methylation, genomic structural variations and microRNAs.

Critical impact on DNA alteration detection, management and treatment of cancer was made by the development of Next-Generation (deep) Sequencing (NGS) technologies which allow a comprehensive molecular profiling of tumors and became a valuable platform for both cancer research and clinical oncology practice.

In a clinical setting, sequencing techniques allow quick identification of druggable molecular alterations, i.e. possible targets for alternative drugs, when standard therapy has failed. Examples of targeted therapies selected based on genomic analyses, include the detection of HER2 amplification in breast cancer, point mutation in BRAF gene in melanoma with their respective inhibitors and many others. Furthermore, NGS is used to analyze liquid biopsies (blood, urine, etc) in cancer diagnostics, disease surveillance and therapeutic response monitoring. In research, identification of alterations in genes driving initial tumor development or metastatic progression, leads to discovery of new targets and novel treatments.

Although powerful, there are weaknesses to NGS as a single approach. A complexity of cancer cells makes identification of specific drivers of cancer growth challenging. Tumor heterogeneity also can be the reason for the lack of response when targeted agents are used. When used for testing of treatment efficacy, NGS technologies can be strengthened if combined with cancer models.

3D cell cultures derived from patients' tumors faithfully recapitulate characteristics of the corresponding parent tumors as exemplified by architectures, the expression of cancer markers, heterogeneity, polarity, cell-cell contact. Tumor microenvironment, an important player in carcinogenesis and treatment response, can also be reconstituted in 3D cultures of cancer organoids which are successfully used in the discovery of personalized anti-cancer therapy and prognostic biomarkers.

Mouse cancer models provide an additional advantage for testing *in vivo* by allowing assessment of toxicities and overall body response. Genetically engineered mice, produced by manipulation of levels of oncogenes and/or deletion of cancer suppressor genes, have been used to study mechanisms of tumorigenesis for decades. More recently, patient-derived xenografts (PDXs), generated from implantation of patient tumor pieces into mice lacking functional immune system, have been successfully developed for a variety of human malignancies. Major applications of PDXs include biomarker discovery, drug testing, elucidation of drug resistance mechanisms and strategies to overcome it.

Integrative approach combining NGS technologies, therapeutic target analyses and drug response monitoring using appropriate cancer model has become an established practice in modern oncology.